USAMRMC

United States Army Medical Research and Materiel Command

Medical Systems Acquisitions

Adenovirus Vaccine Restoration

Adenovirus Vaccine Restoration

Presentation to Armed Forces Epidemiological Board

February 17, 2004

Charles H. Hoke, Jr., M.D.

Medical Advisor, Medical Systems, USAMRMC

Outline

- Historical Review
- Recent AFEB Recommendations
- Current epidemiological situation
- Capability Restoration
  - DOD and Army Requirement
  - Schedule
  - Cost: Financial Plan
  - Performance:
    - Contractor Selection
    - Plant construction
    - Current progress
      - Manufacturing
      - Clinical Development plan
      - Regulatory plan
- Critical Personnel

Historical Review

- ARD in troops: ’50s and ’60s
  - Adenovirus identified as significant contributor
- Adenovirus vaccine invented
  - Safety and efficacy demonstrated
  - Manufactured by Wyeth
  - Used in recruits from 1971
    - Single most important contribution of Medical Research and Development to military readiness.
  - Manufacturing halted 1996
- AFEB Recommendations
- Institute of Medicine Recommendation
- Adenovirus Vaccine Restoration Effort

AFEB Recommendations on Adenovirus Vaccine

Year	Number	Title
2002	02-01	Prevention/Minimization of Adenovirus Infection
1998	98-04	Adenovirus Vaccine
1995	95-01	Recommendations Concerning Adenovirus Vaccine Programs
1991	91-08	DOD Vaccine and Immunization Review - Recommendations Concerning Adenovirus Vaccine
1973	73-09	Live Type 4 and 7 Adenovirus Vaccines
1971	71-10	Live Type 4 and 7 Adenovirus Vaccine
1971	71-02	Vaccination of Air Force Personnel with Oral Live Type 4 Adenovirus Vaccine
1970	70-07	Use of Adenovirus Vaccines and Need for Research
1970	70-04	Procurement and Use of Type 4 Adenovirus Vaccine
1967	67-11	Live Type 4 Adenovirus Vaccine, use of
1966	66-16	Guidelines, Use of Adenovirus Vaccine at Bases during this Fall and Winter
1966	66-03	Live Oral Type 4 Adenovirus Vaccine, Administration of
1965	65-24	Adenovirus Vaccine
1965	65-08	Live Type 4 Adenovirus Vaccine
1965	65-07	Interim Use of Trivalent Inactivated Adenovirus Vaccine
1964	64-16	Use of Live Adenovirus Vaccines
1961	61-01	AFEB Recommendations on Adenovirus Vaccine

Recent AFEB recommendations on Adenovirus Vaccine

NOV 2 3 2001

AFEB (15-1a) 02-01

MEMORANDUM FOR The Assistant Secretary of Defense (Health Affairs)
The Surgeon General, Department of The Army
The Surgeon General, Department of The Navy
The Surgeon General, Department of The Air Force

SUBJECT: Prevention/Minimization of Adenovirus Infection

5. Based on currently available information, the Board makes the following recommendations:

a. THE SINGLE GREATEST PRIORITY IS TO REESTABLISH A STABILE SUPPLY OF ADENOVIRUS VACCINE AS SOON AS POSSIBLE. IT IS UNLIKELY ANY SINGLE INTERVENTION OR COMBINATION OF INTERVENTIONS WOULD BE AS EFFECTIVE IN THE BASIC RECRUIT TRAINING SETTING AS THE ADENOVIRUS VACCINE HAS BEEN IN REDUCING ARI. IT IS UNCLEAR TO THE BOARD WHY IT HAS BEEN ESTIMATED TO TAKE AS LONG AS 6-8 YEARS TO ESTABLISH A NEW SUPPLY OF VACCINE, SINCE THE EXISTING VACCINE IS AN ALREADY FOOD AND DRUG ADMINISTRATION APPROVED AND LICENSED PRODUCT.

AFEB (15-1a) 98-4 09 January 1998

MEMORANDUM FOR THE ASSISTANT SECRETARY OF DEFENSE (HEALTH AFFAIRS)
THE SURGEON GENERAL, DEPARTMENT OF THE ARMY
THE SURGEON GENERAL, DEPARTMENT OF THE NAVY
THE SURGEON GENERAL, DEPARTMENT OF THE AIR FORCE

SUBJECT: Recommendation for the Use of Adenovirus Vaccine

a. EVERY REASONABLE EFFORT BE MADE TO INSURE ADEQUATE AVAILABILITY OF ORAL ADENOVIRUS VACCINE BY:

1) SEEKING AN EXTENSION OF EXPIRATION ON THE CURRENTLY HELD ADENOVIRUS VACCINE LOTS TO THE SPRING OF 1999.

2) IDENTIFYING A MANUFACTURER TO PRODUCE ADEQUATE SUPPLIES OF ADENOVIRUS VACCINE.

AFEB (15-1a) 95-1 28 February 1995

MEMORANDUM FOR THE ASSISTANT SECRETARY OF DEFENSE (HEALTH AFFAIRS)
THE SURGEON GENERAL, DEPARTMENT OF THE ARMY
THE SURGEON GENERAL, DEPARTMENT OF THE NAVY
THE SURGEON GENERAL, DEPARTMENT OF THE AIR FORCE

SUBJECT: Recommendations Concerning Adenovirus Vaccine Program

At its 23-24 February 1995 meeting, the Armed Forces Epidemiological Board was briefed on issues regarding the adenovirus vaccine program. Although a short term critical supply problem appears to have been resolved, the Board has concerns about the long term success of this program. To assist you in prioritizing this program, we discussed these issues and provide the following general comments:

a. THE RISK AND IMPACT OF ADENOVIRUS INFECTIONS TO MILITARY OPERATIONS ARE CONSIDERED OF HIGHEST SIGNIFICANCE AT PRESENT AND FOR THE THE FORESEEABLE FUTURE.

b. ASSURING CONTINUING AND TIMELY AVAILABILITY OF THE CURRENT VACCINE SHOULD BE GIVEN THE HIGHEST PRIORITY IN FACILITATING ACQUISITION.

Institute of Medicine Recommendation

"The committee recommends:

- that a much greater sense of urgency be placed on reacquiring an effective adenovirus vaccine;

- that a significantly larger and long-term commitment be made to restore and maintain the ongoing availability of adenovirus vaccine; and

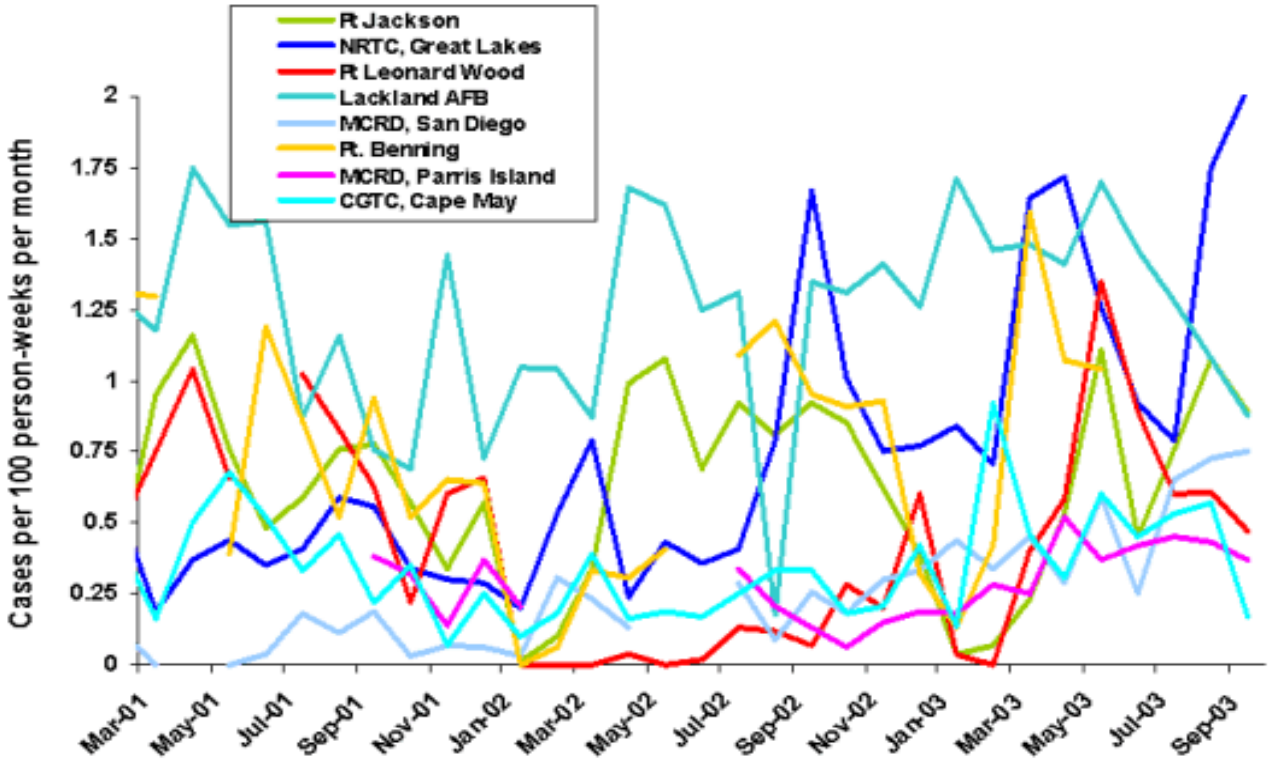
- that the DoD not only evaluate the cause(s) underlying this serious procurement system failure, but also make a clear commitment to the changes necessary to prevent similar breakdowns in the future. "

Current epidemiological situation.

Surveillance methods

- Naval Health Research Center (NHRC): Processes specimens for respiratory virus isolation from Army, Navy, and Air Force Basic Training posts.
- Air Force Institute of Occupational Health (AFIOH): Isolates viruses from specimens from Air Force posts, primarily Lackland Air Force Base.
- Armed Forces Institute of Pathology (AFIP): Assembles pathology information on fatal pneumonia cases in recruits.

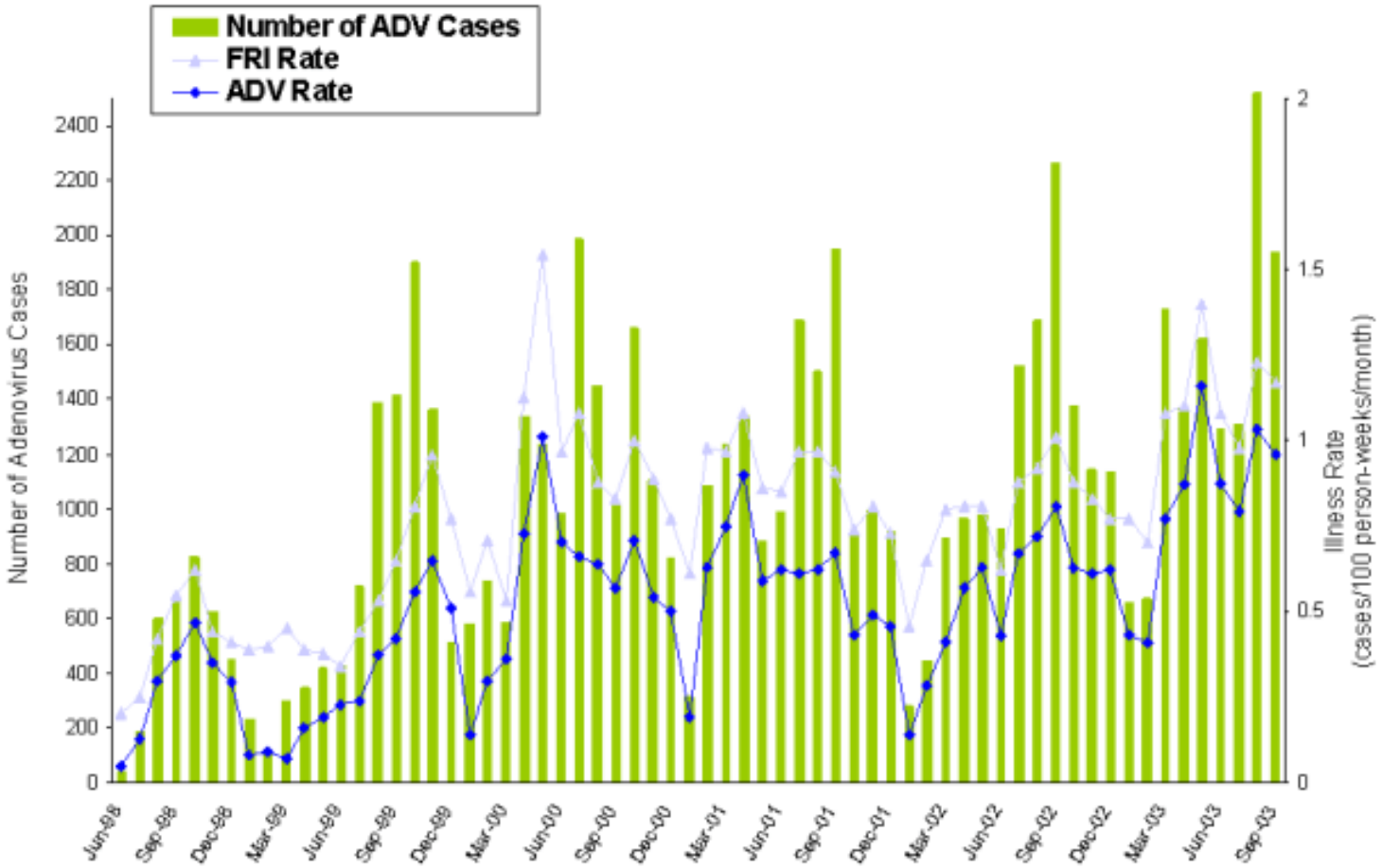
Adenovirus Infection Rates at Basic Training Centers



Courtesy of CDR Kevin Russell
Naval Health Research Center

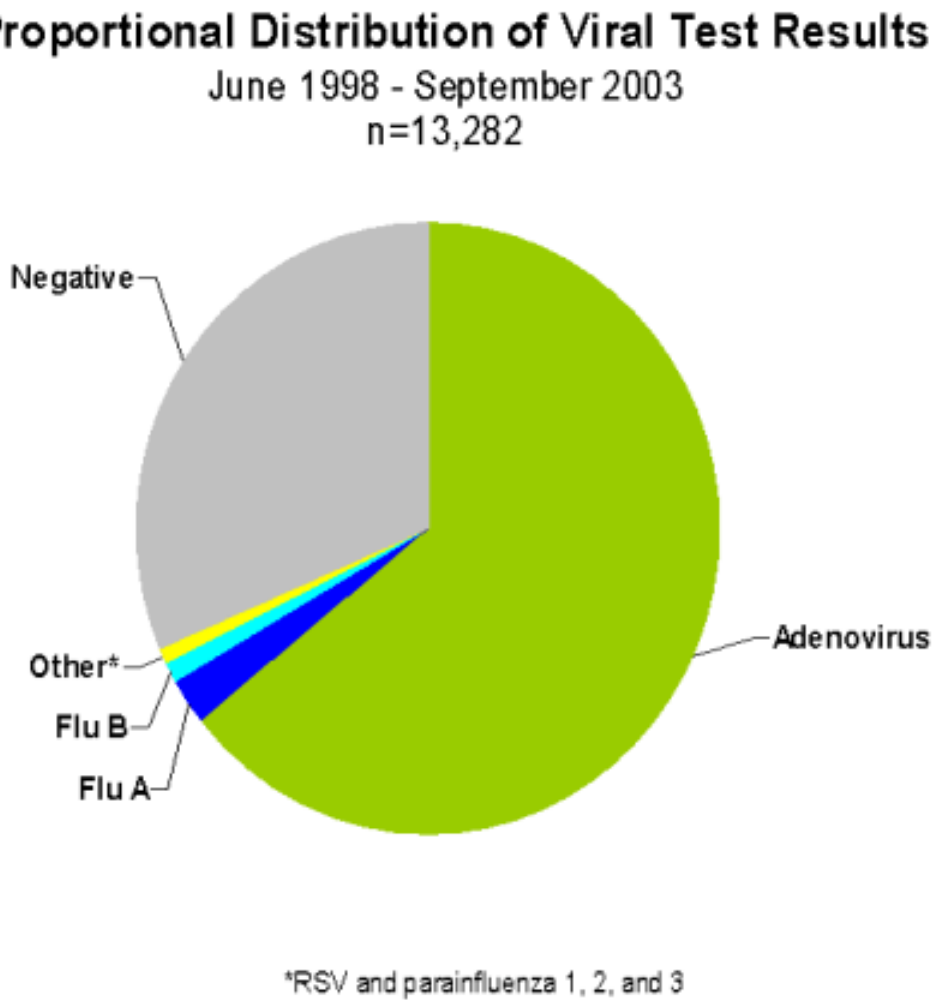
Graph shows continuous isolations of adenovirus (almost all ADV 4) at levels substantially above those observed during use of adenovirus

Adenovirus cases occur seasonally with maximum numbers in September. Rates have gradually risen since 1998.



Courtesy of CDR Kevin Russell
Naval Health Research Center

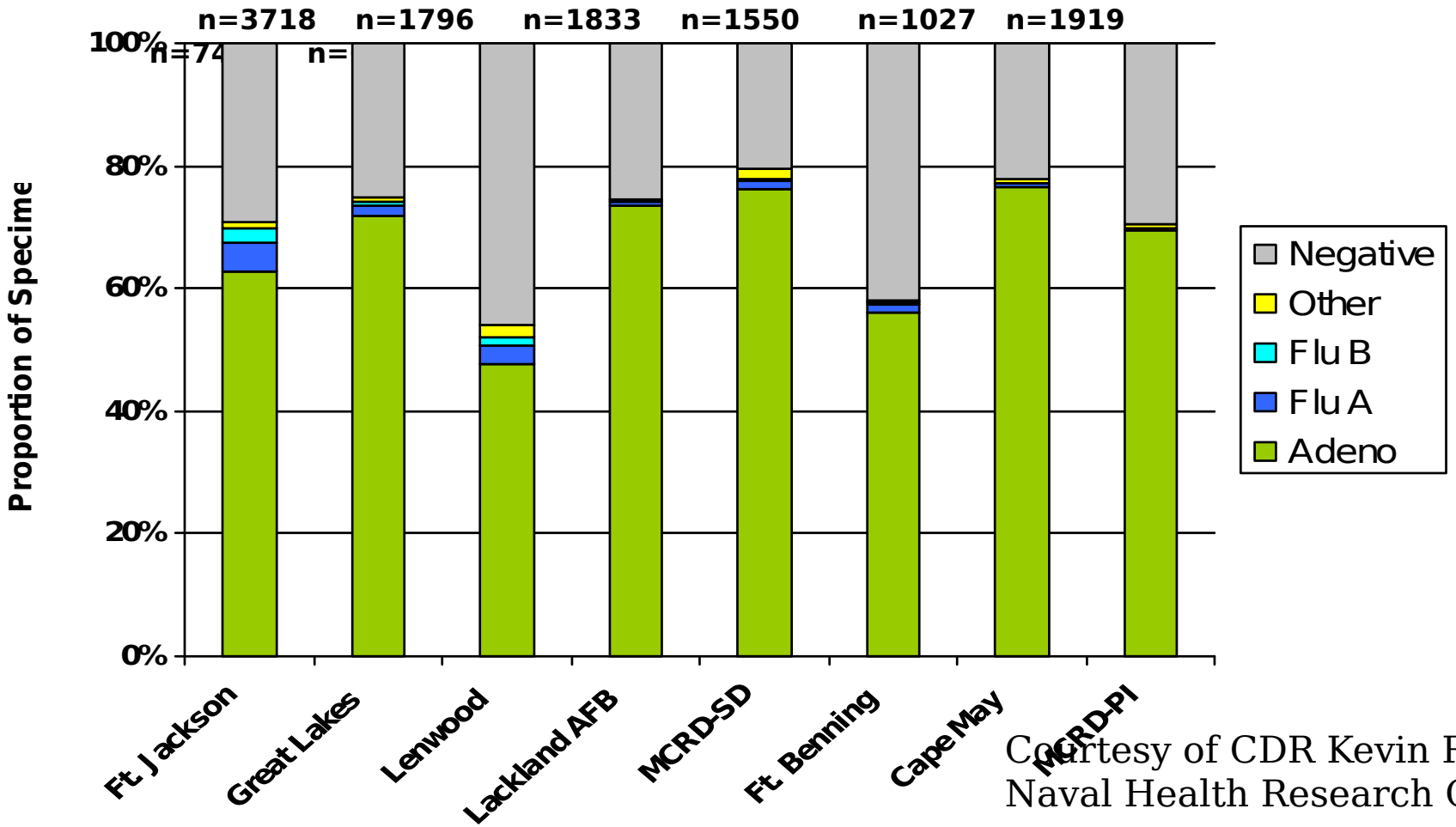
Adenovirus (mainly adenovirus 4) is by far the predominant isolate from recruits with febrile respiratory disease.



Courtesy of CDR Kevin Russell
Naval Health Research Center

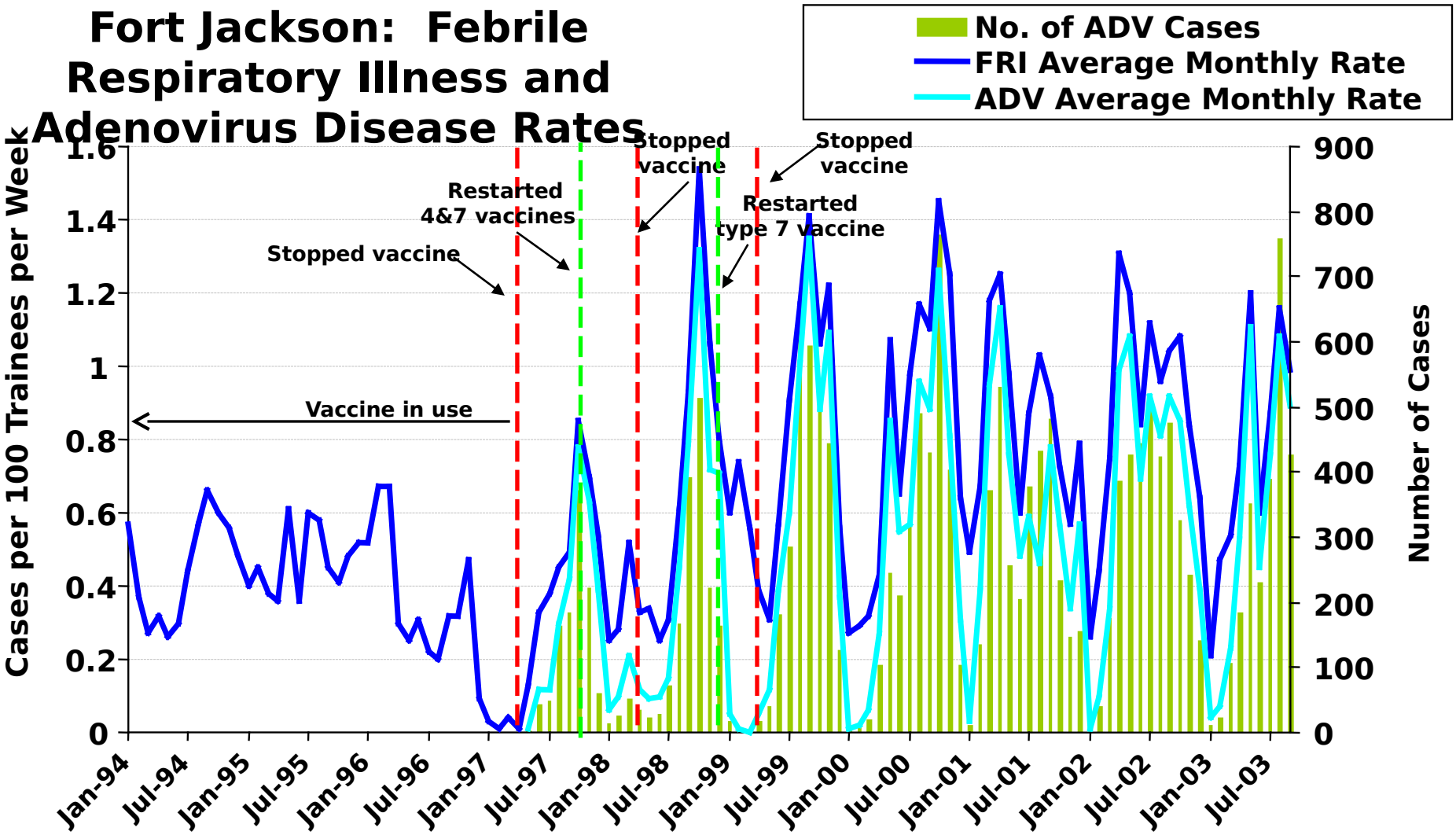
Distribution of Viral Test Results by Site

June 1998 - September 2003
n=13,282



Courtesy of CDR Kevin Russell
Naval Health Research Center

Fort Jackson: Febrile Respiratory Illness and Adenovirus Disease Rates



Specimens positive for adenovirus submitted to AFIOH from Lackland Air Force Base

Season	Submitted	Positive	% positive
’98-’99	314	52	19
’99-’00	3301	1932	59
’00-’01	654	594	91
’01-’02	883	552	63
’02-’03	1046	777	74

Data provided by Angie Owens, Maj Gould, and Linda Canas, Air Force Institute of Operational Health, San Antonio, TX

Note remarkable increase in numbers of adenovirus isolates and in proportion of specimens positive. Anecdotes of hundreds of ill recruits, opening new wards for their care, recycling through training were

8 Fatal adenovirus infections in recruits

1. Dudding BA, Wagner SC, Zeller JA, Gmelich JT, French GR, Top FH Jr. Fatal pneumonia associated with adenovirus type 7 in three military trainees. N Engl J Med. 286:1289-92, 1972.

2. Ryan, M, et al, Two Fatal Cases of Adenovirus-Related Illness in Previously Healthy Young Adults --- Illinois, 2000. MMWR. 50:553-555, 2001.

3. Personal Communication from CDR Kevin Russell, NHRC and MAJ Lisa Pearse, AFIP

A. San Diego Marine male RECRUIT. Died SEPT 03. Work-up positive for: Lungs (2 independent samples): PCR + for Adenovirus Serotype-4, sequence confirmed; lungs (2 independent samples): PCR + for N. meningitidis, and immunohistochemical + for N. meningitidis (performed by CDC). Culture positive for Neisseria species, work-up ongoing.

B. Ft. Sill male RECRUIT. Died NOV 03. Work-up positive for: Lungs: PCR + for Adenovirus Serotype-4 (sequence confirmed); PCR + for Adenovirus Serotype-7 (sequence confirmed); culture + for Adenovirus Serotype-4.

C. Ft. Leonard Wood male RECRUIT, just returned home from training. Died DEC 03. Work-up positive for: Right Lung, Left Lung, Nasal Washings: all PCR + for Adenovirus Serotype-4. Right Lung, Left Lung,

Summary: Adenovirus infections in recruits in 2004.

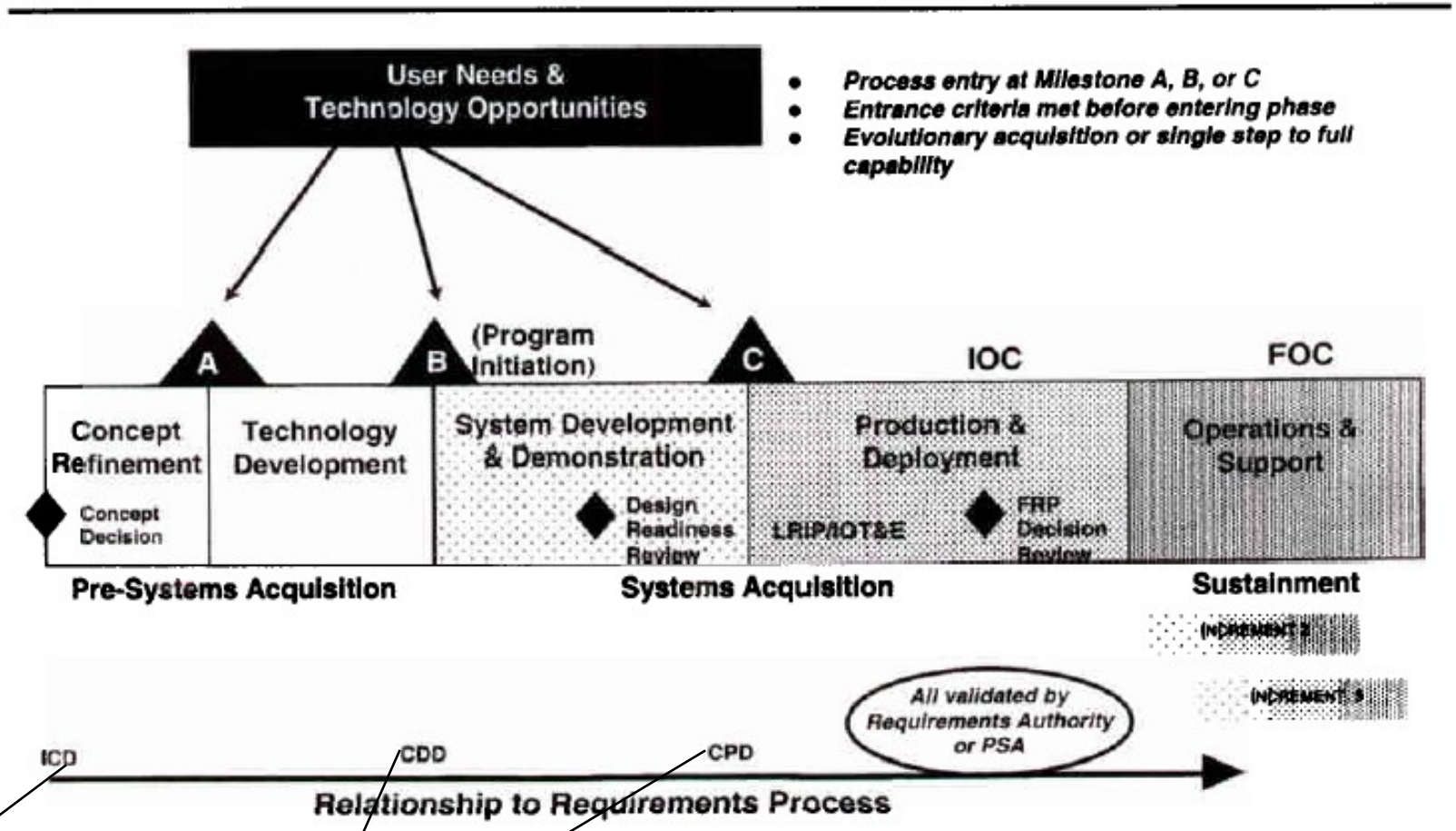
- Rates of febrile respiratory illness on basic training posts continue to be above levels observed when adenovirus vaccine was available.
- Adenovirus isolates are made in large numbers year round, but more especially associated with times during which recruit camps are most crowded (summer and fall).
- Fatalities have been observed from which adenoviruses (usually 4, rarely 7) have been isolated and/or detected by PCR.
- From limited convenience samples, approximately 70% of isolates from recruits febrile respiratory disease are adenoviruses.
- Many isolates have been made from recruits in all three services.

Summary paraphrased from CDR Kevin Russell, NHRC & Linda Canas, AFIOH.

The return of adenovirus disease to recruit camps following withdrawal of licensed adenovirus vaccine is a profound epidemiological demonstration that a

Adenovirus Vaccine Restoration

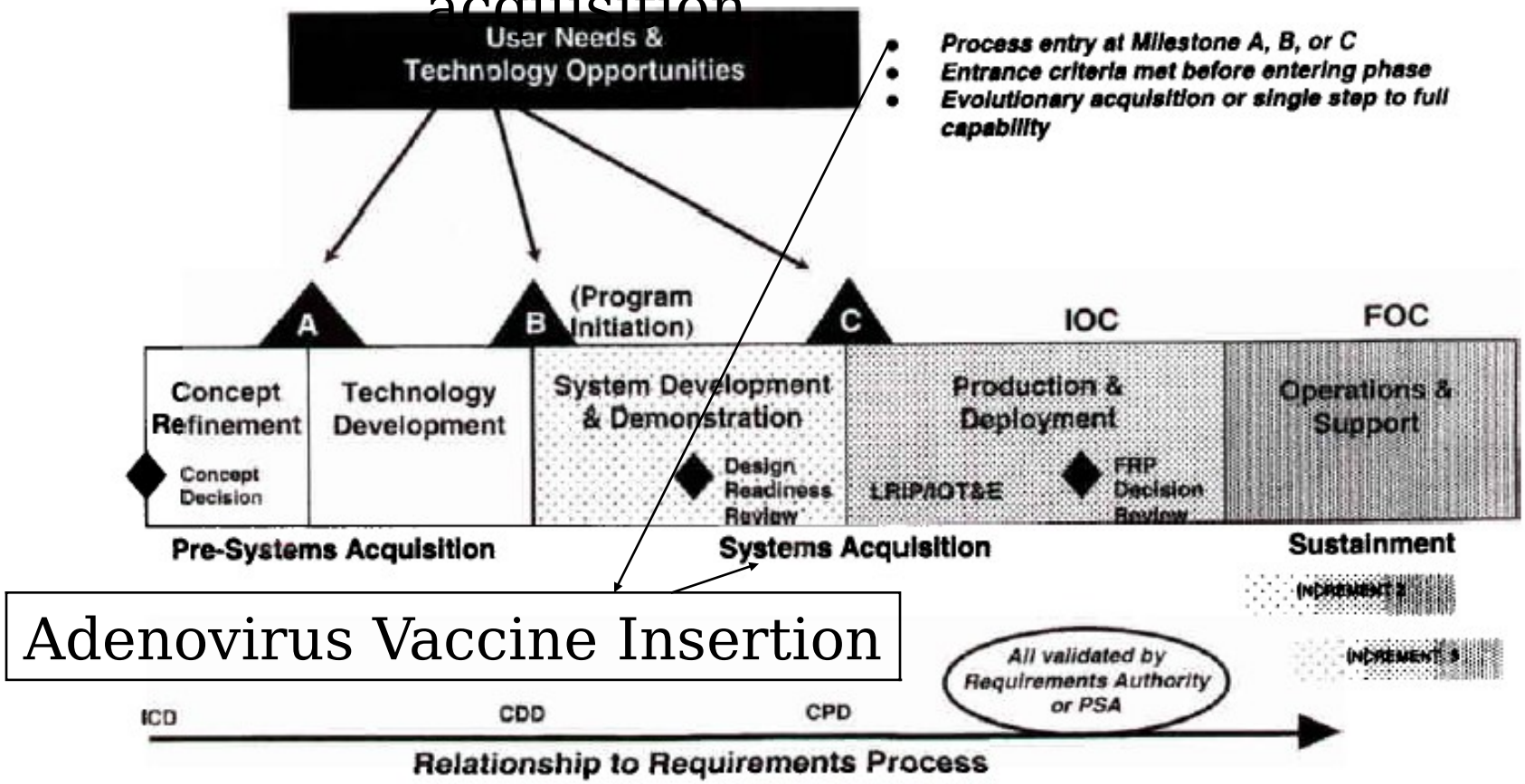
Standard Acquisition Process from AR 70



3–1. The Defense Acquisition Model

ICD: Initial Capabilities Document
CDD: Capability Development Document
CPD: Capability Production Document

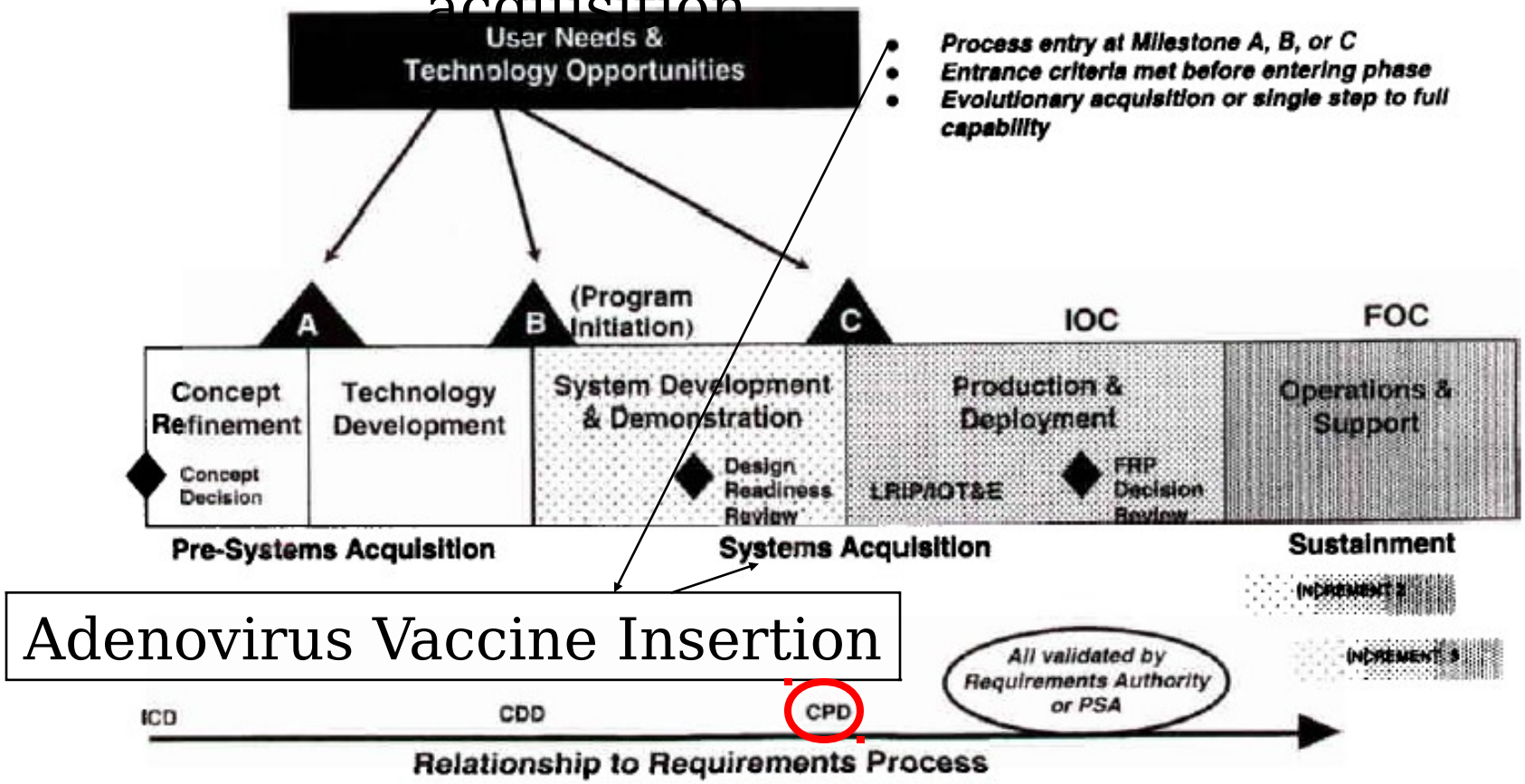
Standard Acquisition Process applied to Adenovirus Vaccine Re-acquisition



3–1. The Defense Acquisition Model

ICD: Initial Capabilities Document
CDD: Capability Development Document
CPD: Capability Production Document

Standard Acquisition Process applied to Adenovirus Vaccine Re-acquisition



ICD: Initial Capabilities Document
CDD: Capability Development Document
CPD: Capability Production Document

3–1. The Defense Acquisition Model

Requirements Documents

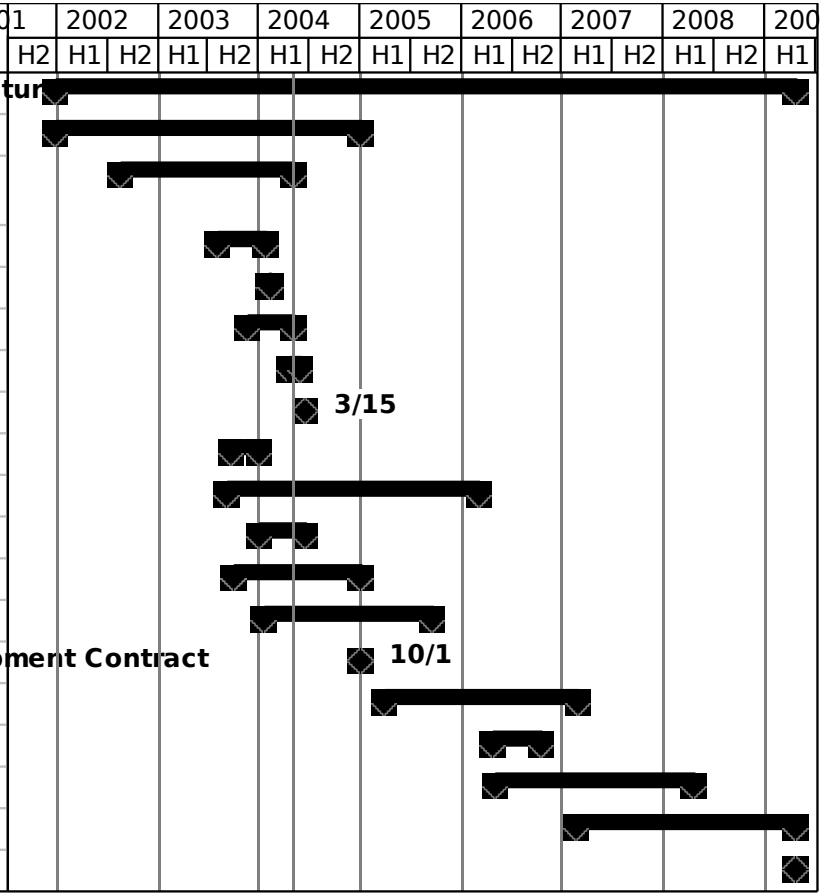
No validated DOD/Army Requirement Document (Capability Production Document) for adenovirus vaccine exists.

DOD and Army Acquisition systems are being updated and precise processes for acquiring Requirements Documents are not in place.

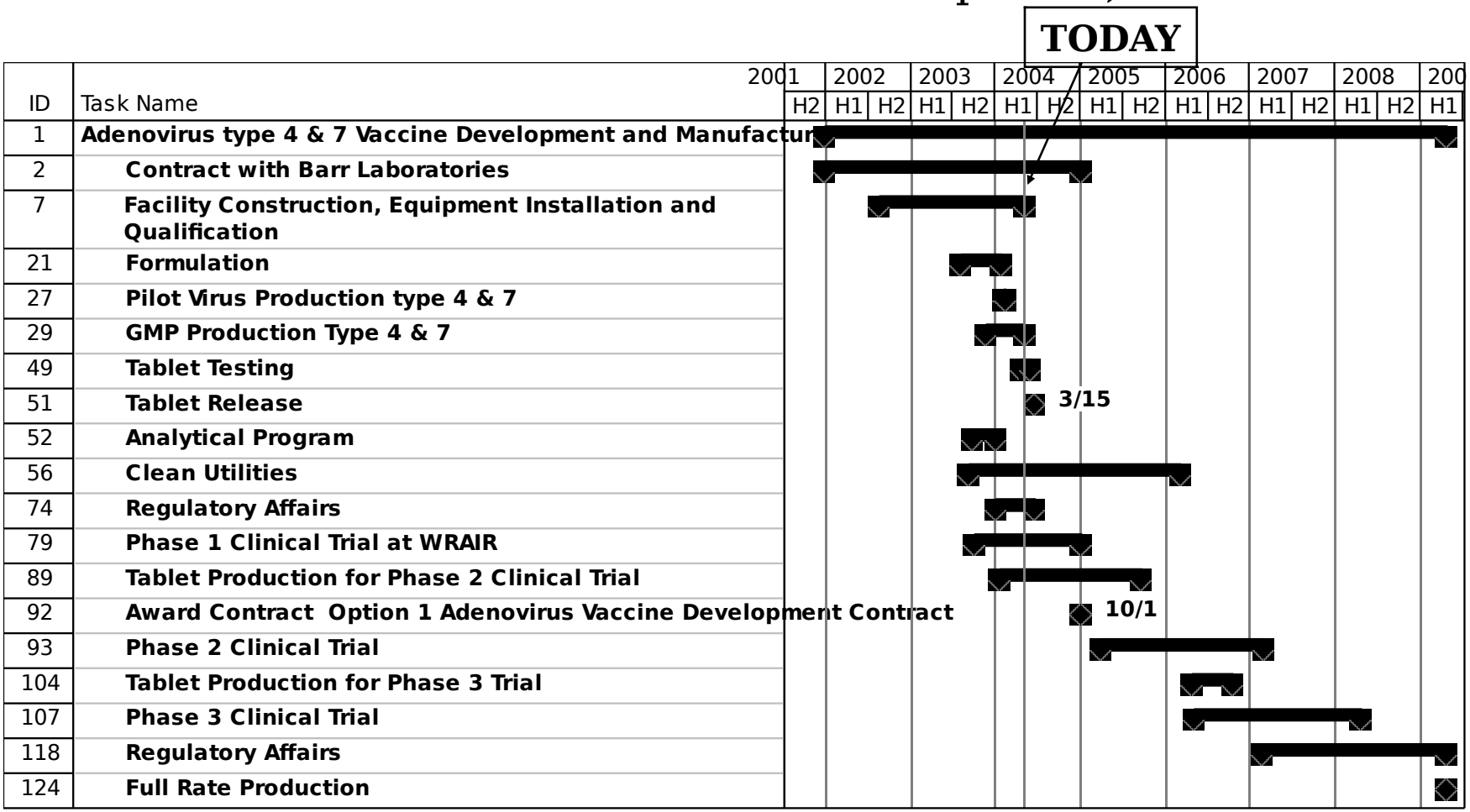
Schedule

Schedule for Adenovirus Vaccine Restoration (Assumes full phase 1-3 clinical trials are required.)

ID	Task Name
1	**Adenovirus type 4 & 7 Vaccine Development and Manufactur**
2	**Contract with Barr Laboratories**
7	**Facility Construction, Equipment Installation and Qualification**
21	**Formulation**
27	**Pilot Virus Production type 4 & 7**
29	**GMP Production Type 4 & 7**
49	**Tablet Testing**
51	**Tablet Release**
52	**Analytical Program**
56	**Clean Utilities**
74	**Regulatory Affairs**
79	**Phase 1 Clinical Trial at WRAIR**
89	**Tablet Production for Phase 2 Clinical Trial**
92	**Award Contract Option 1 Adenovirus Vaccine Development Contract**
93	**Phase 2 Clinical Trial**
104	**Tablet Production for Phase 3 Trial**
107	**Phase 3 Clinical Trial**
118	**Regulatory Affairs**
124	**Full Rate Production**

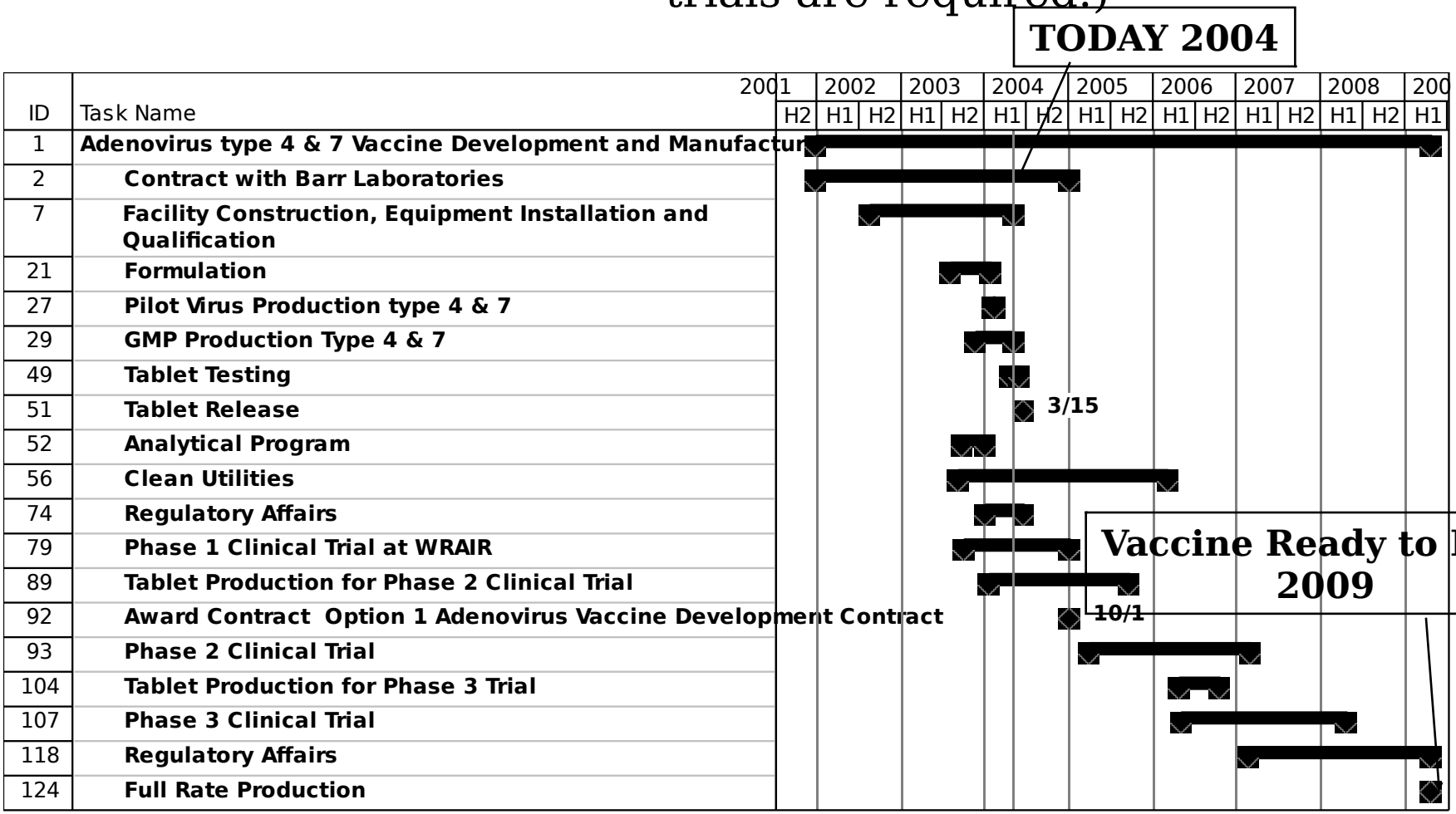


Schedule for Adenovirus Vaccine Restoration (Assumes full phase 1-3 clinical trials are required.)



ID	Task Name
1	**Adenovirus type 4 & 7 Vaccine Development and Manufactur**
2	**Contract with Barr Laboratories**
7	**Facility Construction, Equipment Installation and Qualification**
21	**Formulation**
27	**Pilot Virus Production type 4 & 7**
29	**GMP Production Type 4 & 7**
49	**Tablet Testing**
51	**Tablet Release**
52	**Analytical Program**
56	**Clean Utilities**
74	**Regulatory Affairs**
79	**Phase 1 Clinical Trial at WRAIR**
89	**Tablet Production for Phase 2 Clinical Trial**
92	**Award Contract Option 1 Adenovirus Vaccine Development Contract**
93	**Phase 2 Clinical Trial**
104	**Tablet Production for Phase 3 Trial**
107	**Phase 3 Clinical Trial**
118	**Regulatory Affairs**
124	**Full Rate Production**

Schedule for Adenovirus Vaccine Restoration (Assumes full phase 1-3 clinical trials are required.)



ID	Task Name
1	**Adenovirus type 4 & 7 Vaccine Development and Manufactur**
2	**Contract with Barr Laboratories**
7	**Facility Construction, Equipment Installation and Qualification**
21	**Formulation**
27	**Pilot Virus Production type 4 & 7**
29	**GMP Production Type 4 & 7**
49	**Tablet Testing**
51	**Tablet Release**
52	**Analytical Program**
56	**Clean Utilities**
74	**Regulatory Affairs**
79	**Phase 1 Clinical Trial at WRAIR**
89	**Tablet Production for Phase 2 Clinical Trial**
92	**Award Contract Option 1 Adenovirus Vaccine Development Contract**
93	**Phase 2 Clinical Trial**
104	**Tablet Production for Phase 3 Trial**
107	**Phase 3 Clinical Trial**
118	**Regulatory Affairs**
124	**Full Rate Production**

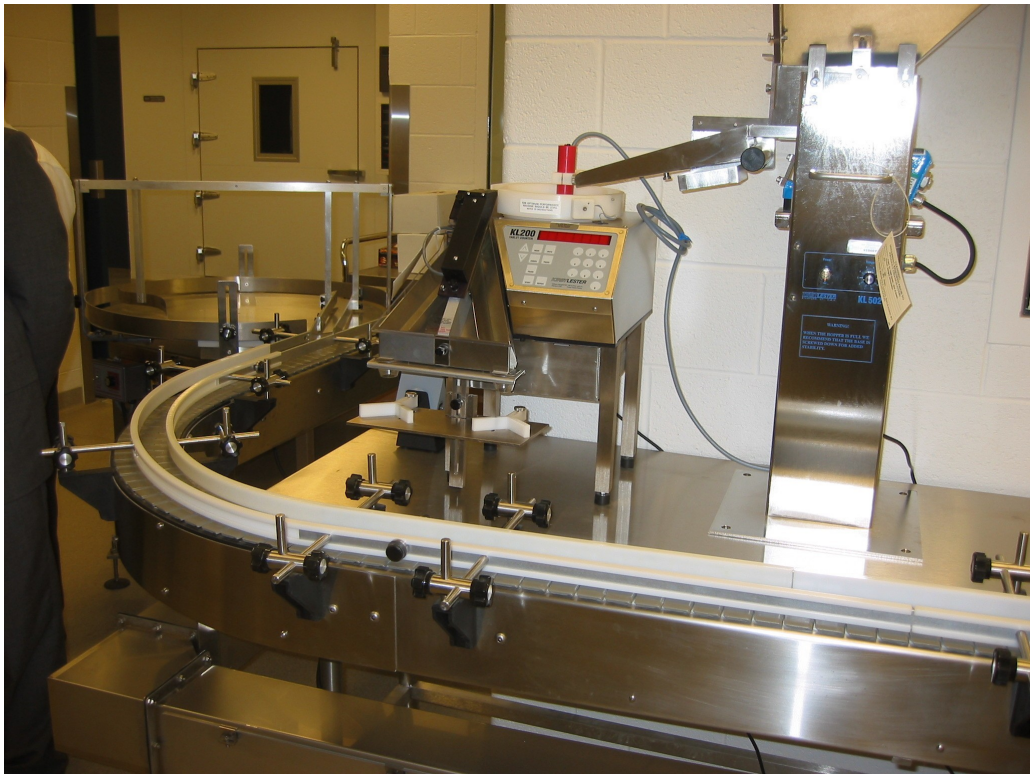
Performance

- Manufacturer Selection
- Transfer of manufacturing methods from Wyeth.
- Progress of manufacturer
  - Plant Construction
  - Pilot lot production
  - Tableting
- Progress at WRAIR/MRMC
  - Product manager assigned.
  - Lyophilization
  - Recent clinical trial with expiring Wyeth vaccine
  - Development of assays to support clinical trials
  - Drafting and review

Adenovirus Vaccine Production Facility

25 July 2003

Vaccine Tableting Equipment



Summary of Contractor's Quarterly Report (Through 31 December 2003)

- Bulk virus production at Q-One
- Formulation and Lyophilization at WRAIR
- Assay Development
- Tablet Production
- Clinical Trials
- DOD issues
- Financial issues

Bulk Virus Production

- Viruses grow sufficiently well in WI-38 cells.
  - ADV 4=6.725 TCID50/ml
  - ADV 7=7.775 TCID50/ml
- Wyeth vaccine was produced on WI-38 cells.
  - Evaluation of MRC-5 cells as alternative is planned.
- Production of ADV-4 and -7 Master Virus Banks was finished in early September 2003.
- ADV-4 and -7 GMP lots for vaccine production initiated September 2003.
  - ADV-4 GMP lot finished in October 2003: titer OK.
    - Transferred to WRAIR for production of lyophilized, stabilized virus sufficient to product tablets for clinical trails.
  - ADV-7 GMP lot harvested in early January 2004.

Formulation and Lyophilization at WRAIR

- Lyophilization process developed last summer based on Wyeth specifications
- Pilot run (no virus) completed.
- Pilot run (non-GMP virus) completed. Trays sent to Barr for tableting in Jan 2004.
- GMP ADV-4 lyophilization produced and stored at WRAIR until GMP tablet production starts in Feb 2004.
- GMP ADV-7 lyophilization scheduled for Feb 5, 2004.

Assay Development

- Assays developed by Barr
  - Moisture, Disintegration, Residual Solvents, Cleaning Agents, Phenol Red
- Antisera for *in vitro* adventitious agents test
  - Must neutralize adenoviruses.
  - Serum provided by Wyeth neutralizes 4&7 at 1:10.
  - Have enough for 2 more lots.
  - Program to make more antisera initiated.
- Method to inactivate virus left on equipment
  - Gives greater than 5 log reduction in titer. (acceptable)

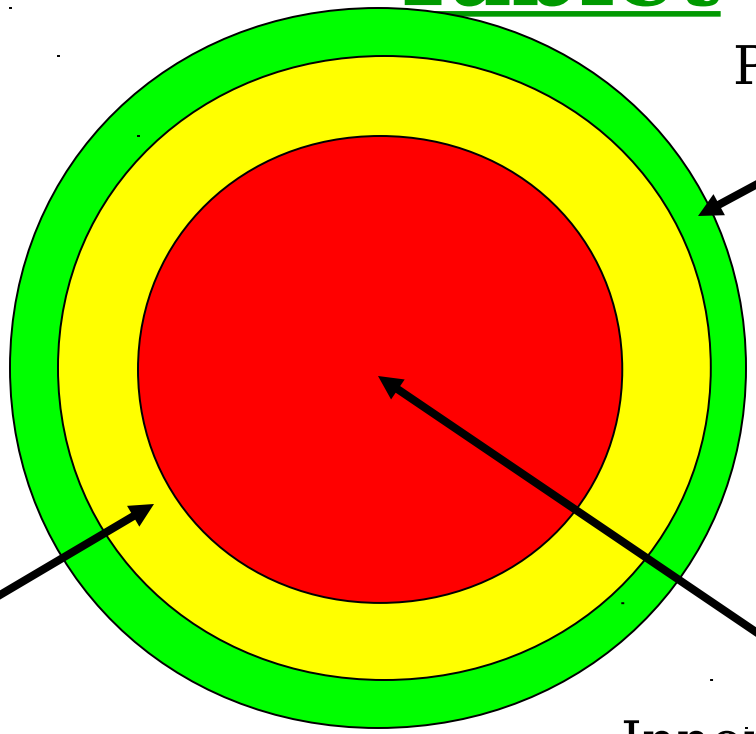
Tablet Production Facility

- Facility in Virginia
  - Completed
  - Equipment installed
  - Qualifications performed
  - Building systems approval dates were provided.
- Produced 5 trial batches with pilot lyophilized material.
- Planning to bring pilot non-GMP lyophilized virus from WRAIR into facility in Jan 2004 for tablet production.
- WRAIR test of new dye in tablet indicates no loss of infectivity (good news)

Mock Adenovirus Vaccine Tablets

First tablets with type 4 live virus made 31 Jan 2004

Adenovirus Vaccine Tablet



Provided by Dr. Andy Towle

Regulatory Strategy

- The replacement vaccine is equivalent to the previously licensed vaccine in all possible specifications.
  - Wyeth provided full access to all manufacturing records.
  - Army retained former FDA reviewer to abstract records.
  - Contract proposals were based on Wyeth procedures.
  - Wyeth pledged to provide all possible assistance to new manufacturer.
- Replacement vaccine specifications will be as close to those of previously licensed vaccine as possible.

Comparison of Barr and Wyeth Adenovirus Vaccines

	Wyeth	Barr	Key Differences	Significance
Cells	Human Diploid (WI-38)	Human Diploid (WI-38)	None	None
ADV 4	ADV4 CL68578 p15	ADV4 CL68578 p15	None	Minimal
ADV 7	ADV7 55142 p16	ADV7 55142 p16	None	Minimal
Cell Growth Media	EMEM +10% FCS + antibiotics	DMEM + 10% FBS	Antibiotics Removed	Minimal
Tablet Dye	FD&C 5 (Tartrazine)	FD&C 6	Dye	None
Potency/Dose	NLT 32,000 TCID 50	NLT 32,000 TCID 50	None	None
Route	Single Oral Tab	Single Oral Tab	None	None

The specifications of the replacement vaccine are designed to be as close to those of the licensed vaccine as possible

Clinical Trials

- Strategy planned on Sept 10 2003 at Barr.
- Phase 1
  - Two groups (30 each)
    - Group 1: Both ADV 4 and ADV 7 tablets
    - Group 2: Placebo.
  - Primary Goal
    - Safety
    - Reactogenicity
  - Secondary Goal
    - Neutralization titer
    - Duration of virus shedding
- Draft Investigator Brochure and Clinical Trial Brochure produced at WRAIR
  - Approved by HSRRB.

Regulatory issues

- A contract modification to allow Barr Laboratories, Inc. to sponsor and file the IND was executed 9 Jan.
- Pre-IND letter has been written for submission to FDA to schedule pre-IND meeting.
  - Currently under review at Contractor.
- FDA comments will be solicited on:
  - Manufacturing plans to produce ADV vaccines comparable to Wyeth vaccines.
  - Proposed clinical trial plan

DOD Issues

- DOD requested Barr to file IND application to FDA.
- Base contract covers manufacture up to the end of phase 1 trial.
- Renewal option covers the phase 2 and 3 trial(s), subject to FDA approval of the plan.

Critical Personnel

- Advisor to ASD(HA)
  - Armed Forces Epidemiological Board
- Requirements
  - Generator:
    - AMEDD Center and School
  - Approval
    - Chief of Staff of Army
    - Joint Requirements Office
- Milestone Decision Authority
  - MG Martinez-Lopez, Commanding General, US Army Medical Research and Materiel Command

Critical Personnel (cont'd)

- Deputy for Acquisitions, USA MRMC
  - Mr. William Howell
- Pharmaceutical Systems Project Manager
  - Dr. Lawrence Lightner
- Product Manager
  - LTC Janet Moser
- Production Consultant
  - TBD
- Army Clinical Director
  - COL Wellington Sun
- Barr/VaccGen Staff (Dr. Towle, Dr. Liss)

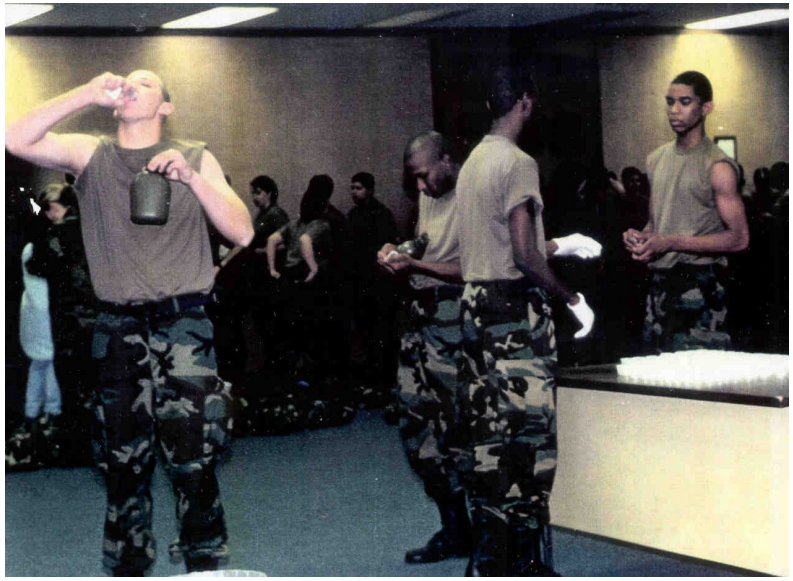
Functions needed for clinical development phase

- Integrated Project Team (IPT) advises Product Manager
- Contractor's Management
- Clinical Development Planning
- Pharmacovigilance
- Protocol Development
- Data Management
- Report Generation
- Quality Assurance
- Data and Safety Monitoring Board

Conclusions

- Adenovirus vaccine restoration program is on schedule to complete first clinical by Fall FY 2004.
- Risks
  - FDA acceptance of the clinical development plan by the FDA is unknown at this time
  - Lack of formal requirements documents may impair continuity
  - DOD contracting may cause unintended delays in process
  - Turnover in DOD acquisition staff may disrupt smooth management
- Advantages
  - WRAIR and Barr are working synergistically.
  - Problems to date have been dealt with successfully.
- Replacement vaccine should be available no later than 2009.

The Goal.



Background Material

Selected Past AFEB and IOM Recommendations on Adenovirus Vaccines

DEPARTMENT OF DEFENSE
ARMED FORCES EPIDEMIOLOGICAL BOARD

AFEB 28 May 1971

THE EXECUTIVE SECRETARY
ARMED FORCES EPIDEMIOLOGICAL BOARD
OFFICE OF THE SURGEON GENERAL
DEPARTMENT OF THE ARMY
WASHINGTON, D.C. 20315

MEMORANDUM FOR: THE SURGEON GENERAL, DEPARTMENT OF THE ARMY
THE SURGEON GENERAL, DEPARTMENT OF THE NAVY
THE SURGEON GENERAL, DEPARTMENT OF THE AIR FORCE

SUBJECT: Live Type 4 and 7 Adenovirus Vaccines

1. The Armed Forces Epidemiological Board, in executive session on 19 May 1971, accepted and approved the following recommendations of the Commission

(A) LIVE ADENOVIRUS TYPE 4 VACCINE SHOULD BE USED IN ALL THREE SERVICES AS REQUIRED TO CONTROL EPIDEMICS IN RECRUITS AND ADVANCED TRAINING PERSONNEL. IT IS ANTICIPATED THAT THE LIVE TYPE 4 VACCINE WILL BECOME LICENSED FOR MILITARY USE IN 1972, AND ORDERS TO PROCURE ADEQUATE SUPPLY FOR USE BY THE THREE SERVICES IS RECOMMENDED. CONTINUED SURVEILLANCE REGARDING THE NEED FOR AND EFFECT OF THE VACCINE SHOULD BE CONTINUED WHEREVER POSSIBLE.

(B) LIVE TYPE 7 ADENOVIRUS VACCINE SHOULD BE USED TO DETERMINE ITS CLINICAL EFFECTIVENESS.

(C) USE OF TYPES 4 AND 7 ADENOVIRUS VACCINES MAY ENCOURAGE THE EMERGENCE OF OTHER ADENOVIRUSES AS EPIDEMIC STRAINS. IT IS RECOMMENDED, THEREFORE, THAT EXPERIMENTAL DEVELOPMENT AND SUBSEQUENT USE, IF NECESSARY, OF VACCINES CONTAINING ADENOVIRUS TYPE 14 AND 21 SHOULD BE ENCOURAGED.

(D) AN ACCELERATED INVESTIGATION OF CAPSID PROTEIN VACCINES FREE OF VIRAL DNA SHOULD BE CONDUCTED. IF SUBUNIT VACCINE IS AN EFFECTIVE IMMUNOGEN, FIELD TESTS SHOULD BE CARRIED OUT, AND IF THE RESULTS WARRANT IT, THE VACCINE SHOULD BE DEVELOPED FOR USE.

2. Dr. Ginsberg has made a matter of record his uneasiness and concern about the use of live adenovirus vaccines, particularly that containing type 7 virus, except for experimental purposes. Despite absence of evidence that adenovirus is oncogenic in man, negative data are difficult to evaluate. It is known that there are no sensitive methods to detect the oncogenic potential of an agent in man. The dangers involved may be as great as those of some chemicals whose use in man has been banned on the basis of animal experimentation.

FOR THE ARMED FORCES EPIDEMIOLOGICAL BOARD:

BRADLEY M. PRIOR
Colonel, USAF, MC
Executive Secretary

Copy furnished:
Board Members
Commission Directors
Deputy Directors
ASD (H&E) 2
Chiefs Prev Med Div, D/A, D/N, D/AF (4)

DEPARTMENT OF DEFENSE
ARMED FORCES EPIDEMIOLOGICAL BOARD
5109 LEESBURG PIKE
FALLS CHURCH, VA 22041-3258

AFEB (1S-1a) 95-1 28 February 1995

MEMORANDUM FOR THE ASSISTANT SECRETARY OF DEFENSE (HEALTH AFFAIRS)
THE SURGEON GENERAL, DEPARTMENT OF THE ARMY
THE SURGEON GENERAL, DEPARTMENT OF THE NAVY
THE SURGEON GENERAL, DEPARTMENT OF THE AIR FORCE

SUBJECT: Recommendations Concerning Adenovirus Vaccine Program

At its 23-24 February 1995 meeting, the Armed Forces Epidemiological Board was briefed on issues regarding the adenovirus vaccine program. Although a short term critical supply problem appears to have been resolved, the Board has concerns about the long term success of this program. To assist you in prioritizing this program, we discussed these issues and provide the following general comments:

a. THE RISK AND IMPACT OF ADENOVIRUS INFECTIONS TO MILITARY OPERATIONS ARE CONSIDERED OF HIGHEST SIGNIFICANCE AT PRESENT AND FOR THE FORESEEABLE FUTURE.

b. ASSURING CONTINUING AND TIMELY AVAILABILITY OF THE CURRENT VACCINE SHOULD BE GIVEN THE HIGHEST PRIORITY IN FACILITATING ACQUISITION.

c. ALTERNATIVE SCENARIOS FOR THE USE OF VACCINE SUCH AS OUTBREAK CONTROL SHOULD BE CONSIDERED AND RESEARCH TO DETERMINE THE RELATIVE EFFICACY OF SUCH PROGRAMS SHOULD BE CONDUCTED.

d. LONG TERM ARRANGEMENTS TO ASSURE A STABLE AND RELIABLE SOURCE OF VACCINE SHOULD BE PURSUED VIGOROUSLY.

e. EPIDEMIOLOGIC SURVEILLANCE ACTIVITIES INCLUDING DIAGNOSTIC CAPABILITIES SHOULD BE STRENGTHENED IN THE MILITARY.

AFEB (1S-1a) 95-1 28 February 1995

SUBJECT: Recommendations Concerning the Adenovirus Vaccine Program

LEWIS H. KULLER, M.D., DrPH
President, AFEB

for MICHAEL R. PETERSON, DVM, MPH, DrPH
Colonel, USAF, BSC
Executive Secretary

Copies Furnished:

ASD(HA)
HQDA/SG
HQUSAF/SG
BUMED/SG
Board Members
Ch, HQ, USAF, SGP
Ch, Prev Med Div, OTSG-DA
Ch, Prev Med Div, OTSG-DAF
Dir, Occup Hlth & Prev Med Div, BUMED-OM
DASD (PA&QA)
DASD (Medical Readiness)
Dir, AFIP
Dir, AFMIC
Cmdr, U. S. Army Med R&D Cmd
CO NAVMEDRSCHDEVCOM
Navy Env. Health Center (Code 36)
Dir, Prof Svcs, OTSG-DA
Dir, Med Resources, Plans & Policy Div. (N931)
Dir, Env. Life Sci., OUSDA, ATTN: Dr. J. Osterman
ASBREM Sec., R&D, NMC
Head, Epi Dept., NEPMU 5
COL Francis O'Donnell, USA, MC
CDR Timothy J. Ungs, USPHS
COL Robert Leitch, RAMC
CDR Gordon Clifford, CFMS

USAMRMC

DEPARTMENT OF DEFENSE
ARMED FORCES EPIDEMIOLOGICAL BOARD
5109 LEESBURG PIKE
FALLS CHURCH, VA 22041-3258

REPLY TO ATTENTION OF

AFEB (15-1a) 98-4 09 January 1998

MEMORANDUM FOR THE ASSISTANT SECRETARY OF DEFENSE (HEALTH AFFAIRS)
THE SURGEON GENERAL, DEPARTMENT OF THE ARMY
THE SURGEON GENERAL, DEPARTMENT OF THE NAVY
THE SURGEON GENERAL, DEPARTMENT OF THE AIR FORCE

SUBJECT: Recommendation for the Use of Adenovirus Vaccine

1. The Infectious Disease Control Subcommittee of the Armed Forces Epidemiological Board (AFEB) has had the opportunity to examine adenovirus surveillance data and outbreak epidemiologic data. Based on (a) the known risk of recurrent adenovirus outbreaks, and (b) the substantial morbidity of adenovirus outbreaks, including disruption of recruit training, and (c) the substantial costs in treating adenovirus infections and the associated follow-on respiratory infections (e.g. increased risk of streptococcal and pneumococcal infections), the Infectious Disease Subcommittee recommends that:

a. EVERY REASONABLE EFFORT BE MADE TO INSURE ADEQUATE AVAILABILITY OF ORAL ADENOVIRUS VACCINE BY:

1) SEEKING AN EXTENSION OF EXPIRATION ON THE CURRENTLY HELD ADENOVIRUS VACCINE LOTS TO THE SPRING OF 1999.

2) IDENTIFYING A MANUFACTURER TO PRODUCE ADEQUATE SUPPLIES OF ADENOVIRUS VACCINE.

b. CONCOMITANT WITH THE ABOVE, THE INFECTIOUS DISEASE SUBCOMMITTEE RECOMMENDS THAT ALL RECRUITS RECEIVE THIS VACCINE IN TRAINING SETTINGS WITH KNOWN OUTBREAKS OF ADENOVIRUS ILLNESS ON A YEAR-ROUND BASIS WHEN VACCINE IS AVAILABLE.

c. THAT CONTINUED AND ONGOING SURVEILLANCE OF ADENOVIRUS SEROTYPES BE CARRIED OUT IN RECRUIT TRAINING SETTINGS.

d. THAT ADDITIONAL DISEASE CONTROL METHODS FOR THE PREVENTION OF ADENOVIRUS OUTBREAKS BE PURSUED.

AFEB (15-1a) 98-4 09 January 1998
SUBJECT: Recommendation for the Use of Adenovirus Vaccine

2. The above recommendation was approved by both the Infectious Disease Subcommittee and the full Board on 12 December 1997.

FOR THE ARMED FORCES EPIDEMIOLOGICAL BOARD:

GERALD F. FLETCHER, M.D.
AFEB President

VICKY L. FOGELMAN
Colonel, BSC, USAF
AFEB Executive Secretary

Copies Furnished:

The Surgeon General, USA
The Surgeon General, USAF
The Surgeon General, USN
Board Members
DASG-ZH
AFMOA/CC
Ch, Prev Med Div, OTSG-DA
Ch, Prev Med Div, OTSG-DAF
Dir. Occup Hlth & Prev Med Div, BUMED-DN
CDR, WRAIR
CDR, USAMEDCOM, ATTN: MCHO-CL-W
CDR, USACHPPM, ATTN: MCHB-DP
CDR, U.S. MRMC-ZA
Navy Env. Health Center
Dir, Med Resources, Plans & Policy Div. (N931)
Head, Epi Dept., NEPMU 5
CDR Barbara A. Braden, USCG
COL Andrew S. Warde, BvetMed Msc MRCVS
LCOL Frank Souter, CFMS

USAMRMC

DEPARTMENT OF DEFENSE
ARMED FORCES EPIDEMIOLOGICAL BOARD
5109 LEESBURG PIKE
FALLS CHURCH VA 22041-3258

NOV 2 3 2001

AFEB (15-1a) 02-01

MEMORANDUM FOR The Assistant Secretary of Defense (Health Affairs)
The Surgeon General, Department of The Army
The Surgeon General, Department of The Navy
The Surgeon General, Department of The Air Force

SUBJECT: Prevention/Minimization of Adenovirus Infection

1. On 18 September 2001 the Armed Forces Epidemiological Board (AFEB) was presented with a request from the Assistant Secretary of Defense for Health Affairs (ASD(HA)) to provide recommendations on non-vaccine methods to minimize and control the transmission of adenoviral and other acute respiratory disease-causing agents in the recruit training setting. To assist the Board, the Preventive Medicine officers from the Army, Navy, Air Force, and Coast Guard presented data on respiratory disease incidence at the Service recruit training centers. Dr. Larry J. Anderson from the Division of Viral and Rickettsial Diseases, Centers for Disease Control and Prevention (CDC), presented to the Board CDC's experience with adenovirus outbreaks.

2. The Board continues to be deeply concerned about the loss of adenovirus vaccine for use in the basic training setting and the resultant increase in acute respiratory illnesses (ARI) among basic trainees at several basic training sites across the military services. The rates of ARI and disease impact appear to be uneven from site to site, but sustained increases in disease have been observed since the loss of the adenovirus vaccine at several U.S. Army basic training posts, Great Lakes Naval Training Center, Lackland Air Force Base, and the U.S. Coast Guard Training Center Cape May. Increased ARI in the basic training setting is far more than an inconvenience. It has resulted in increased utilization of outpatient medical care, increased numbers of hospitalizations, one to several missed days of training for affected recruits and resultant "recycling" of some basic trainees, and most tragically, two adenovirus related deaths among U.S. Navy recruits.

3. Recent events in New York, Washington DC, and Pennsylvania, as well as the numerous anthrax cases, carry the potential for a protracted military response over the coming months and years. This may result in increased numbers of basic trainees processing through existing recruit training sites which are already at times overcrowded. This combination of factors increases the likelihood for even greater problems associated with ARI than currently observed, as ARI transmission is enhanced by crowded conditions. ***Therefore, the Boardfeels that this issue goes beyond traditional public health concerns and should be viewed as having the potential to jeopardize operational military readiness, as it did in the early and mid-20th century.***

AFEB (15-1a) 02-01
SUBJECT: Prevention/Minimization of Adenovirus Infection

4. There appears to be a wealth of historical epidemiologic data, both from studies done in the pre-vaccine era and from studies of more recent outbreaks. In addition, there are intriguing patterns suggesting significant differences in the incidence of ARI across the basic training sites. It is possible that some of these differences are explained by differential case ascertainment and application of case-definition, but these are unlikely to explain the magnitude of the differences. Well designed and executed hypothesis driven research studies examining potential factors associated with endemic and epidemic disease occurrence in some settings, and the lack of epidemic disease in others, clearly need to be performed.

5. Based on currently available information, the Board makes the following recommendations:

a. THE SINGLE GREATEST PRIORITY IS TO REESTABLISH A STABILE SUPPLY OF ADENOVIRUS VACCINE AS SOON AS POSSIBLE. IT IS UNLIKELY ANY SINGLE INTERVENTION OR COMBINATION OF INTERVENTIONS WOULD BE AS EFFECTIVE IN THE BASIC RECRUIT TRAINING SETTING AS THE ADENOVIRUS VACCINE HAS BEEN IN REDUCING ARI. IT IS UNCLEAR TO THE BOARD WHY IT HAS BEEN ESTIMATED TO TAKE AS LONG AS 6-8 YEARS TO ESTABLISH A NEW SUPPLY OF VACCINE, SINCE THE EXISTING VACCINE IS AN ALREADY FOOD AND DRUG ADMINISTRATION APPROVED AND LICENSED PRODUCT.

b. THE BOARD IS CONCERNED THAT AN EXAMINATION OF NON-VACCINE/NON-ANTIMICROBIAL METHODS TO REDUCE ARI TRANSMISSION, WHILE UNDERSTANDABLE IN THE ABSENCE OF ADENOVIRUS VACCINE, MAY RESULT IN A PERCEPTION BY THE MILITARY SERVICES THAT THESE METHODS REDUCE THE URGENCY OF OBTAINING A SUPPLY OF ADENOVIRUS VACCINE, AND MIGHT EVEN SUBSTITUTE FOR IT AND OTHER VACCINES. EVEN FOR THE BEST STUDIED AND MOST WIDELY USED OF THESE PRACTICES ▪ HAND WASHING AND BUNK SPACING ▪ THERE IS LIMITED EVIDENCE THAT NON-VACCINE METHODS ARE EFFECTIVE. MUCH OF THAT EVIDENCE IS OLD AND MAY NOT BE VALID IN THE CURRENT RECRUIT TRAINING ENVIRONMENT. NON-VACCINE METHODS ARE FLAWED BECAUSE THEY ABSOLUTELY DEPEND ON THEIR CONSCIENTIOUS, CONTINUOUS, AND PERSISTENT APPLICATION. THE CULTURE NECESSARY TO ACHIEVE THIS IS EXTREMELY DIFFICULT TO SUSTAIN UNDER THE PRESSURES AND DEMANDS OF RECRUIT TRAINING, AND THE CONTINUOUS TURNOVER OF THOSE WHO **CONDUCT THE TRAINING. THEREFORE, THE BOARD EMPHASIZES THAT NON-VACCINE/NON-ANTIMICROBIAL METHODS ARE NEVER A SUBSTITUTE FOR VACCINES AND ARE, AT BEST, A STOP-GAP MEASURE.**

USAMRMC

AFEB (15-la) 02-01
SUBJECT: Prevention/Minimization of Adenovirus Infection

c. RESEARCH EFFORTS SHOULD BE DIRECTED TOWARDS THE STUDY OF ANTIMICROBIAL/ANTIVIRAL COMPOUNDS AND VACCINES OTHER THAN ADENOVIRUS, MENINGOCOCCAL, AND INFLUENZA WHICH MAY BE EFFECTIVE FOR PREVENTION, PROPHYLAXIS OR TREATMENT OF ARI IN THE RECRUIT SETTING INCLUDING DISEASE OUTBREAKS.

d. AMONG ALTERNATIVE COUNTERMEASURES (ADMINISTRATIVE, PERSONAL HYGIENE, ENVIRONMENTAL, AND ENGINEERING), THE TWO THAT APPEAR TO HAVE BEEN THE BEST STUDIED AND HOLD THE MOST PROMISE IN REDUCING THE BURDEN OF ARI ARE HANDWASHING/PERSONAL HYGIENE AND BUNK SPACING. HOWEVER, MANY OF THE STUDIES ON THESE MEASURES TOOK PLACE DECADES AGO, AND IT IS UNCLEAR HOW APPLICABLE THEY ARE TO TODAY'S MILITARY BASIC TRAINING SETTING. A DETAILED REVIEW OF THE HISTORICAL AND CURRENT DATA ON THESE TWO INTERVENTIONS (INCLUDING SPECIFIC STUDIES AND OUTBREAK INTERVENTIONS) SHOULD BE CONDUCTED, SUMMARIZED INTO A SINGLE DOCUMENT, AND PRESENTED TO THE BOARD IN ORDER THAT MORE SPECIFIC RECOMMENDATIONS FOR THEIR APPLICATION IN THE BASIC TRAINING SETTING CAN BE MADE.

e. IF A RECOMMENDATION IN FAVOR OF ANY OF THE ABOVE COUNTERMEASURES IS MADE, THERE MUST BE A MECHANISM AND THE NECESSARY RESOURCES AVAILABLE TO ASSURE THEY ARE APPROPRIATELY ADOPTED AND IMPLEMENTED BY THE VARIOUS SERVICES AND AT ALL MILITARY BASIC RECRUIT TRAINING SITES.

f. PENDING MORE SPECIFIC RECOMMENDATIONS, ALL BASIC TRAINING SITES SHOULD PROVIDE AMPLE OPPORTUNITIES FOR AND ENCOURAGE FREQUENT HAND WASHING (OR COMPARABLE METHODS) AND PERSONAL HYGIENE AMONG BASIC TRAINEES. ALL SITES SHOULD PROVIDE TISSUES TO TRAINEES TO COVER THEIR NOSES AND MOUTHS WHEN SNEEZING OR COUGHING, AND ALLOW TISSUES TO BE CARRIED AS NECESSARY. ATTITUDES AND BARRIERS THAT DISCOURAGE THESE ACTIVITIES SHOULD BE ELIMINATED BY COMMAND POLICY AND COMMAND ENFORCEMENT.

g. OTHER COUNTERMEASURES (E.G. BENZATHINE PENCILLIN FOR CIRCUMSTANCES OTHER THAN CONTROLLING GROUP A STREPTOCOCCAL DISEASE, ENHANCED VENTILATION, ULTRAVIOLET LIGHT) APPEAR TO HAVE BEEN BENEFICIAL IN LIMITED CIRCUMSTANCES OR HAVE NOT BEEN DEMONSTRATED TO BE EFFECTIVE. THE BOARD IS CONCERNED THAT ANY

AFEB (15-1a) 02-01
SUBJECT: Prevention/Minimization of Adenovirus Infection

7. The above recommendations were unanimously approved.

FOR THE ARMED FORCES EPIDEMIOLOGICAL BOARD:

STEPHEN M. OSTROFF, M.D.
AFEB, President

JAMES R. RIDDLE, D.V.M., M.P.H.
Lt Col, USAF, BSC
AFEB Executive Secretary

Encl
ASD(HA) Memorandum dated 8 August 2001

CF:
Board Members and Consultants (w/encl)
USAMRMC (w/encl)
USAMRIID (w/encl)
USD (AT&L) (w/encl)
Joint Vaccine Acquisition Program (w/encl)
J4-MRD (w/encl)

Urgent Attention Needed to Restore Lapsed Adenovirus Vaccine Availability

A Letter Report

November 6, 2000

Major General John Parker
Commanding General
U.S. Army Medical Research and Materiel Command
Fort Detrick, MD 21702-5012

Dear General Parker:

In April 2000, the Institute of Medicine of the National Academies convened an expert committee to advise the U.S. Army Medical Research and Materiel Command on the management of natural infectious disease threats to the military. The Committee on a Strategy for Minimizing the Impact of Naturally Occurring Infectious Diseases of Military Importance: Vaccine Issues in the U.S. Military will issue its complete report in January 2002. At its initial three meetings, the committee reviewed the failure of the Department of Defense (DoD) to maintain a supply of the adenovirus vaccine as an example of the problems DoD faces regarding the licensure, manufacture, and maintenance of special use vaccines. Production of this vaccine ceased in 1996 and stocks were depleted in 1999. What the committee heard was extremely disconcerting with respect to the threat that the lack of this vaccine now poses to the health of recruit populations. The committee submits this interim letter report today with a sense of extreme urgency in an effort to reinforce the view that there is a critical need for the DoD to expeditiously reestablish a process for the licensure, manufacture, purchase, and

distribution of the adenovirus vaccine to military personnel undergoing recruit training activities.

The committee found:

- that the adenovirus vaccine is urgently needed to control the epidemic respiratory disease that has caused much morbidity among recruits in the past, and now once again threatens the health and even the lives of military trainees; since acute pulmonary infection due to adenovirus is a nearly unique occupational risk of the military trainee, it is imperative that DoD take rapid and effective action to once more eliminate this preventable disease;
- that the short-term, $14 million Defense Health Program commitment to acquiring an adenovirus vaccine is insufficient to stimulate the interest of capable commercial vaccine manufacturers; and
- that the existing acquisition and procurement systems within DoD are not structured to ensure continuing availability of limited use vaccines.

The committee recommends:

- that a much greater sense of urgency be placed on reacquiring an effective adenovirus vaccine;
- that a significantly larger and long-term commitment be made to restore and maintain the ongoing availability of adenovirus vaccine; and
- that the DoD not only evaluate the cause(s) underlying this serious procurement system failure, but also make a clear commitment to the changes necessary to prevent similar breakdowns in the future. In its final report to you, this committee will address system issues in depth in an attempt to help the Department of Defense define and then resolve the problem.

The basis for these findings and recommendations is presented in the text that follows.

INTRODUCTION

Capping 30 years of military medical research, the licensure of adenovirus type 4 and type 7 oral vaccines was a great success story. Epidemics of severe acute respiratory disease (ARD) had been a leading cause of hospitalization among recruits in Army, Navy, and Marine Corps training installations. In 1971, the first year of widespread use, adenovirus vaccines prevented an estimated 27,000 military hospitalizations. The risk of the severe ARD epidemics of the 1950s and 1960s was abolished. The impact of the vaccines, including a reduced need to recycle trainees who missed critical training due to hospitalization, as

well as savings in the costs of medical care, made the vaccines extremely cost effective.[1]

As a result of a series of decisions that were made beginning in 1984 by Food and Drug Administration regulators, the manufacturer, and DoD officials, the sole manufacturer, Wyeth-Lederle Vaccines, ceased production of adenovirus vaccines in 1996.[2] Discussions between DoD and the manufacturer between 1984 and 1996 failed to lead to a mutually acceptable agreement that would have allowed continued vaccine availability. No alternative source of the vaccine has been found. The military was the only purchaser of adenovirus vaccine and limited its use to recruits in training operations; no civilian market exists at present for this vaccine.

IMPACT ON THE ARMED FORCES

Military surveillance data show minimal adenovirus-related morbidity during the period when the adenovirus vaccine was available and used at the training installations, followed by increased infection rates and hospitalization as vaccine administration became limited and finally ceased. Between October 1996 and May 1998, among symptomatic trainees at four sites, those who did not receive type 4 and 7 vaccine were 13 times more likely to have a positive adenovirus culture and 28 times more likely to be positive for type 4 or 7 adenovirus.[3] Ft. Jackson, Ft. Gordon, NTC Great Lakes, Cape May, Ft. Leonard Wood, Lackland AFB, and, most recently, Ft. Benning, have reported adenovirus epidemics, some with serious morbidity. Some epidemics have required adjustments such as the realignment of resources to convert barracks to infirmaries, the opening of new infirmary wards, the cancellation of elective surgeries, and staffing shifts. A few training camps have seen increases—20-fold at one base—in recruit recycling, when recruits miss enough of the training program that they need to begin again. The published surveillance data graphically show the temporal relationship between vaccine administration and respiratory disease rates in training camps.[4]

[1]Russell PK. Adenovirus infection is not trivial. *U.S. Medicine*, November 1998.

[2]Barraza EM, Ludwig SL, Gaydos JC, Brundage JF. Reemergence of adenovirus type 4 acute respiratory disease in military trainees: Report of an outbreak during a lapse in vaccination. *Journal of Infectious Diseases* 179, 1999.

[3]Gray GC, Goswani PR, Malasig MD, Hawksworth AW, Trump DH, Ryan MA, Schnurr DP (for the Adenovirus Surveillance Group). Adult adenovirus infections: Loss of orphaned vaccines precipitates military respiratory disease epidemics. *Clinical Infectious Diseases* 31:663-670, September 2000.

[4]Gray et al., *ibid.*

In the 1950s and 1960s, before military scientists identified the causative viruses and developed this effective and safe oral vaccine,[5,6,7] approximately 50 percent of recruits fell ill with acute respiratory disease, with certain sites reporting 80 percent attack rates in some years. The vaccine program cut those rates, and the associated hospitalizations, in half. A 1998 cost-effectiveness analysis, using incidence data, a range of vaccination policy options, and medical and training cost data, estimated a savings of approximately $16 million per year were the DoD to reinstate the vaccine program.[8]

CURRENT DEVELOPMENT EFFORT

Attempts by the DoD to find an alternative solution, including initial negotiations with another vaccine manufacturer, have been unsuccessful to date. To restart an adenovirus-vaccine program, the new manufacturer must go through the full FDA new-product approval process. With a one-time $14 million investment from the Defense Health Program, the Medical Research and Materiel Command is preparing a Request for Proposals (RFP). Challenges include creating a contract strategy, with elements such as commitments to multi-year funding, to which manufacturers might respond. DoD anticipates releasing the RFP for comments in the fall of 2000, working toward the best-and-final offer stage in January 2001. Even without schedule slippage, a vaccine will not be available for use within the next three years.[9] The initial funding amount likely will cover only Phase I preparation and some administrative and technical support.[10]

[5]Top FH Jr, Grossman RA, Bartelloni PJ, Segal HE, Dudding BA, Russell PK, Buescher EL. Immunization with live types 7 and 4 adenovirus vaccines. I. Safety, infectivity, antigenicity, and potency of adenovirus type 7 vaccine in humans. *Journal of Infectious Diseases* 124(2):148, August 1971.

[6]Rose HM, Lamson TH, Buescher EL. Adenoviral infection in military recruits: Emergence of type 7 and type 21 infections in recruits immunized with type 4 oral vaccine. *Arch Environ Health* 21:356, September 1970.

[7]Takafuji ET, Gaydos JC, Allen RG, Top FH Jr. Simultaneous administration of live, enteric-coated adenovirus types 4, 7, and 21 vaccines: Safety and immunogenicity. *Journal of Infectious Diseases* 140(1):48, July 1979.

[8]Howell MR, Nang RN, Gaydos CA, Gaydos JC. Prevention of adenoviral acute respiratory disease in Army recruits: Cost-effectiveness of a military vaccination policy. *American Journal of Preventive Medicine* 14(3), 1998.

[9]Howell W. Adenovirus history. Presentation to the Institute of Medicine Committee on a Strategy for Minimizing the Impact of Naturally Occurring Infectious Diseases of Military Importance: Vaccine Issues in the U.S. Military, September 2000.

[10]Howell W. Personal communication, October 2000.

DISCUSSION

- The DoD urgently needs adenovirus vaccine to (a) prevent increasingly large epidemics of febrile illness that put military personnel at risk of illness and even death,[11,12] and (b) avoid costs associated with medical care and disrupted or lost training days due to adenovirus illness.
- The military acquisition and procurement system has proven itself incapable of maintaining continuous availability of the adenovirus vaccine, and, in the opinion of the committee, its structure is inadequate to avoid similar failures for other limited use vaccine products.
- Although the commitment of $14 million of Defense Health Program funding is welcome, it is clearly not sufficient to reestablish licensure and ensure continued manufacture and purchase of an adenovirus vaccine. It seems unlikely that a commitment of this magnitude will be sufficient to bring competent, experienced manufacturers of vaccines into the negotiation process. The likelihood of restoring adenovirus vaccine to the military is significantly threatened by the lack of a longer range funding commitment.
- Reinstating the adenovirus vaccine program would be cost-effective. The monetary benefits of this vaccine's use unequivocably outweigh the high initial expenditures.

♦ ♦ ♦ ♦ ♦ ♦ ♦

Military service places young recruits in a uniquely high-risk setting for adenovirus infections during their training. Therefore, the Department of Defense has an obligation to protect recruits against this well-defined and largely preventable infection. To date, military training operations have not been perceived as significantly affected by adenovirus vaccine unavailability, as indicated by the relative lack of attention given the situation by upper-level commanders. However, the ongoing health surveillance, epidemiology, and military preventive medicine networks have gathered incontrovertible evidence of an impending public health emergency.

Sincerely,

Stanley M. Lemon, M.D. (*Chair*), for the Institute of Medicine
Committee on a Strategy for Minimizing the Impact of Naturally Occurring
Infectious Diseases of Military Importance: Vaccine Issues in the U.S. Military

[11] Levin S, Dietrich J, Guillory J. Fatal nonbacterial pneumonia associated with Adenovirus type 4: Occurrence in an adult. *Journal of the American Medical Association* 201:975, 1967.

[12] Dudding B, Wagner S, Zeller J. Fatal pneumonia associated with adenovirus type 7 in three military trainees. *New England Journal of Medicine* 286:1289, 1972.

INSTITUTE OF MEDICINE • 2101 Constitution Avenue, N.W. • Washington, DC 20418

NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the committee responsible for the report were chosen for their special competences and with regard for appropriate balance.

Support for this project was provided by the U.S. Army Medical Research and Materiel Command under Contract No. DAMD17-00-C-0003. The views, opinions, and/or findings contained in this report are those of the Institute of Medicine Committee on a Strategy for Minimizing the Impact of Naturally Occurring Infectious Diseases of Military Importance: Vaccine Issues in the U.S. Military and should not be construed as an official Department of the Army position, policy, or decision unless so designated by other documentation.

Additional copies of this report are available in limited quantities from the Medical Follow-up Agency, 2101 Constitution Avenue, N.W., Washington, DC 20418. The full text of this report is available on line at **www.nap.edu.**

For more information about the Institute of Medicine, visit the IOM home page at **www.iom.edu.**

Printed in the United States of America.

Two recent fatal cases

Ryan, M, et al, Two Fatal Cases of Adenovirus-Related Illness in Previously Healthy Young Adults --- Illinois, 2000. MMWR. 50:553-555, 2001.

Adenoviruses are common pathogens that often are associated with respiratory and gastrointestinal illness and/or conjunctivitis in young persons. Adenovirus serotypes 4 and 7 have caused outbreaks of self-limited febrile respiratory illness in young adults in basic military training. During the 1950s and 1960s, up to 10% of recruits were infected with adenovirus, and these pathogens were responsible for approximately 90% of pneumonia hospitalizations (*1*). Beginning in 1971, all military recruits received oral, live, enteric-coated vaccines that were licensed by the Food and Drug Administration as safe and effective in preventing illness from adenovirus serotypes 4 and 7. In 1996, the sole manufacturer ceased production of adenoviral vaccines and, as supplies dwindled during the next few years, outbreaks of adenoviral respiratory illness reemerged in military settings (*2*). Since 1999, approximately 10%--12% of all recruits have become ill with adenovirus infection in basic training, similar to the prevaccine era. This report describes the first two deaths probably associated with adenovirus infection identified in military recruits since the vaccines became unavailable. The military has requested proposals for a new adenovirus vaccine manufacturer; however, these deaths suggest that efforts by policymakers and pharmaceutical companies to reestablish adenoviral vaccine production

Characterization of serologic and virologic responses of healthy, adult volunteers to the licensed, live adenovirus vaccines

Study conducted by COL Robert Kuschner
Data provided by COL Wellington Sun

Trial of Previously Licensed Wyeth Adenovirus Vaccine

- Investigator: COL Robert Kuschner
- Conducted: 1997
- Vaccines (Both vaccines administered orally to all subjects)
  - Adenovirus 4 FDA Approved Vaccine
  - Adenovirus 7 FDA Approved Vaccine
- Purpose of trial: To provide benchmark for comparison with replacement vaccine
- Location: WRAIR
- Subjects: Healthy adults
- Endpoints:
  - Virus neutralizing antibody
  - Reported symptoms

Results of trial

- Subjects
  - 40 enrolled
    - 4 developed antibody between the time of screening and the time of vaccine administration.
    - 1 lost to followup.
    - 35 analyzed.
      - Antibody status before immunization:
        - Both 4 and 7: 0
        - Neither 4 nor 7: 8
        - 4 only: 5
        - 7 only: 22
      - Total starting without type 4 antibody: 30
      - Total starting without type 7 antibody: 13

Seroconverters following immunization with Wyeth Vaccine

- Adenovirus 4
  - Seronegative (SN*<2): n=30
  - Seroconverters: 27 (90%)
- Adenovirus 7
  - Seronegative (SN(2): n=13
  - Seroconverters: 13 (100%)

*SN=Serum Neutralizing Antibod

Distribution of adenovirus antibody at day 28 following oral immunization

	Ratio of day 28 titer:day titer					
	Indeterminate	>2	>4	>8	>16	>32
A 4	3	5	10	2	8	2
A 7	0	1	0	0	2	10

Adenovirus excretion following immunization

	Fecal Culture Positive	Throat Culture Positive
A 4	30/30	0/30
A 7	13/13	0/13

Samples were cultured on days 3, 7, 10, 14, 21, 28

Adverse events following immunization with previously licensed Wyeth adenovirus vaccine

	N=35 Subjects
Feverishness	3
Nasal Conjestion	12
Sore Throat	6
Cough	6
Vomiting	1
Diarrhea	8

Total of mild, moderate or severe symptoms recorded in volunteer diaries.